CME

Prevention of Alzheimer disease

Encouraging evidence

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ABSTRACT

OBJECTIVE To review the evidence regarding prevention of Alzheimer disease (AD) in order to highlight the role of family medicine.

QUALITY OF EVIDENCE Most of the evidence relating to prevention of AD is derived from observational (cross-sectional, case-control, or longitudinal) studies. Evidence from randomized controlled trials (RCTs) is available only for blood pressure control and for hormone replacement therapy for menopausal women.

MAIN MESSAGE Many preventive approaches to AD have been identified, but no RCTs support their efficacy. Evidence from RCTs supports the effectiveness of blood pressure control in reducing incidence of AD, but demonstrates that postmenopausal women's use of estrogen is ineffective in reducing it. Observational studies suggest that some preventive approaches, such as healthy lifestyle, ongoing education, regular physical activity, and cholesterol control, play a role in prevention of AD. These approaches can and should be used for every patient because they carry no significant risk. Currently, no effective pharmacologic interventions have been researched enough to support their use in prevention of AD.

CONCLUSION Health professionals should educate patients, especially patients at higher risk of AD, about preventive strategies and potentially modifiable risk factors.

RÉSUMÉ

OBJECTIF Faire le point sur les données concernant la prévention de la maladie d'Alzheimer (MA) afin de préciser le rôle du médecin de famille.

QUALITÉ DES PREUVES Les preuves concernant la prévention de la MA proviennent pour la plupart d'études observationnelles (transversales, rétrospectives ou longitudinales). Les preuves qui proviennent d'essais randomisés avec témoins (ERT) concernent seulement le contrôle de la tension artérielle et l'hormonothérapie de substitution pour les femmes ménopausées.

PRINCIPAL MESSAGE Diverses mesures ont été suggérées pour prévenir la MA, mais aucun ERT n'a démontré leur efficacité. Les données provenant de ces ERT indiquent que le contrôle de la tension artérielle est efficace pour réduire l'incidence de la MA, alors que l'oestrogénothérapie substitutive post-ménopausique ne l'est pas. Les études observationnelles suggèrent que certaines mesures préventives telles qu'un mode de vie sain, l'acquisition de nouvelles connaissances, la pratique régulière de l'exercice et le contrôle du cholestérol jouent un rôle pour prévenir la MA. Toutes ces mesures peuvent et doivent être utilisées dans chaque cas puisqu'elles ne comportent pas de risque appréciable. Jusqu'à présent, aucune intervention pharmacologique n'a fait l'objet de recherche suffisante pour affirmer son utilité comme moyen de prévention.

CONCLUSION Le professionnel de la santé devrait renseigner ses patients, notamment ceux qui présentent un risque élevé de MA, sur les stratégies préventives et la possibilité de modifier les facteurs de risque.

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While there are treatments for Alzheimer disease (AD), it is clear that they have substantial limitations, including the inability to delay progression of disease. It could be that the most efficacious strategy for combating AD is to prevent, or at least delay, onset of clinically significant symptoms. An ideal approach to preventing AD would be easily available, have no risks, be applicable to the entire population, and have evidence from randomized controlled trials (RCTs) of its efficacy for decreasing incidence of AD.

Unfortunately, prevention trials are difficult to conduct because they require large numbers of participants and long periods of follow up.[1] Some preventive approaches can be used for most of the population; others (more expensive, less available, or carrying their own risks to health) would probably be indicated only for those at higher risk of AD. Determining individual risk of developing AD is likely to be important in determining the level of risk or cost individuals are willing to assume in attempting to prevent AD. The aim of this paper is to review the evidence regarding prevention of AD in order to highlight the role of family medicine.

Quality of evidence

Relevant papers were identified by searching MEDLINE from January 1995 to December 2004 using the key words Alzheimer, dementia, and risk and prevention. Specific factors were further sought using the key words blood pressure, diet, cholesterol, education, estrogen, physical activity, risk, prevention, Alzheimer, and dementia. Most of the evidence relating to preventing AD is derived from observational reports of cross-sectional, case-control, or longitudinal (eg, cohort) studies. Evidence from RCTs is available only for blood pressure control and hormone replacement therapy (HRT) for menopausal women.

Initial identification of those at higher risk of AD

Age is clearly a great risk factor for AD. Awaiting older age before initiating preventive interventions, however, would theoretically remove the opportunity to intervene earlier in the disease process. Finding additional risk factors can be helpful from both clinical and research points of view for identifying those at higher risk of developing AD.

The first step in determining risk of AD is likely a good history. The most important risk factors, increases in risk, and levels of evidence supporting them are shown in **Table 1.**[2-26]

Secondary risk assessment

Much research has been done on tests to identify early markers of AD or characteristics that could identify those who will develop AD in the future. Currently, no tests have adequate research into their safety and predictive ability to allow their widespread use in the general population; neuropsychologic or cognitive tests are most frequently used. Patients at higher risk of AD, such as those with family history who are concerned about their risk of AD and those complaining of cognitive or memory problems (especially if these problems are confirmed by family members), should be referred for cognitive testing.

Cognitive testing. Patients usually have mild cognitive impairment (MCI) before they have enough clinical symptoms for physicians to diagnose AD.

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis
Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study
Level III: Expert opinion or consensus statements

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Table 1. Risk factors for Alzheimer disease: *Level of evidence for all items was II.*

RISK FACTOR	RISK OR PREVALENCE
First-degree relative with dementia	RR 2.5-3.5 if a parent or sibling has AD[2,3]
Genotype epsilon 4/4	OR 11.2[4]
Down syndrome	Studies show great variability: prevalence of dementia 4%-88%[5]; 28% had severe cognitive deterioration on 4-year follow up of people with Down syndrome >30 y; prevalence increases with age[6]
Lower educational attainment	OR 11.7 for no education compared with >3 years' education[7]
Exposure to pesticides	RR 2.39 for AD[8]
Traumatic brain injury	OR 1.58 (15 case-control studies[9])
Elevated thyroid-stimulating hormone level	OR 3.8 for dementia[10]
Reduced thyroid-stimulating hormone level	OR 3.5 for AD[11]
Hypertension	OR 1.97 for AD[12,13]
Hypercholesterolemia	OR 2.3 for dementia[14]
Elevated homocysteine level	RR 1.4[15]
Diabetes mellitus	RR 1.3[16]-1.65[17] for AD
Stroke	RR 1.6[18]
Parkinson disease	Three times more dementia[19]; eight times higher incidence of AD in elderly people with most rapid progression of Parkinson symptoms during 8-year follow up[20]
History of major depressive episode	RR 2-4[21-24]; 13% increased risk of dementia with each episode leading to admission[25]
Mild cognitive impairment	Conversion rate of 10%/y[26]

AD—Alzheimer disease, OR—odds ratio, RR—relative risk.

Neuropsychologic tests, principally tests of verbal episodic memory (especially delayed recall tests that ask patients to learn a list of words and recall them later), have been found to be particularly useful in early detection of AD and can help physicians discriminate between patients with mild AD and normal controls.[27,28] These tests have also proven useful for predicting dementia after up to 5 years of follow up.[29]

Patients presenting with subjective cognitive complaints in the absence of demonstrable impairment on testing do not appear to be at increased risk of AD. Patients with MCI, cognitive deficits that manifest only in the context of detailed clinical interviews or neuropsychologic tests, who are generally able to carry out all activities of daily living with no functional impairment, are at increased risk of developing dementia. Rates of progression to dementia vary according to the criteria used for MCI and the source of subjects.[30] A meta-analysis including 1616 subjects found a mean annual conversion rate from MCI to dementia of 10%, compared with a mean incidence of dementia in the general population of 1.82% for the same mean age (74 years).[26]

Trials are now being conducted to establish the effect of treatment with anticholinesterase medications and estrogens in this population. As with most other potential predictors of AD, MCI has high false-positive and false-negative rates for predicting future onset of AD. Also, MCI might simply be an immediately preclinical phase of AD. An ideal preventive approach would probably be started even before onset of MCI.

Neuroimaging. Much research is being done with neuroimaging as well. Hippocampal and entorhinal cortex atrophy on magnetic resonance imaging studies, reduced blood flow and reduced glucose metabolism in temporoparietal and posterior cingulate areas on positron emission tomography (PET) and single proton emission computed tomography (SPECT) studies were demonstrated in patients with MCI and are increasingly well established risk factors for subsequent development of AD in this population.[31-36] These findings, however, are not specific enough to be useful as predictors of AD in the general population. Long-term prospective follow-up studies are needed to establish the value of neuroimaging measures as early markers or predictors of AD.

Genetic testing. Genetic factors have an important role in pathogenesis of AD. Several genes are known to be involved: the APP gene on chromosome 21, the PSEN1 gene on chromosome 14, and the PSEN2 gene on chromosome 1 are responsible together for 6% to 7% of all cases of AD, especially early-onset cases (<65 years).[37] More is also known about the complex etiology of late-onset AD. The major susceptibility gene—apolipoprotein E (APOE) located on chromosome 19—has been confirmed in numerous studies.[38,39] While the epsilon

4 allele of APOE is the most common identifiable genetic risk factor for late-onset AD, it is not yet useful for clinical purposes because its positive and negative predictive rates in the general population are unacceptably low. As with other types of testing, positive predictive rates for genetic testing will improve if the tests are done on populations at increased risk of AD (eg, based on history).

Preventive approaches: modifiable risk factors

Many risk factors are potentially modifiable and might have a role in preventing AD.

Blood pressure control. High blood pressure was identified as a risk factor for AD in a large epidemiologic study (odds ratio [OR] 1.97, confidence interval [CI] 1.09 to 3.54) with a dose-response effect: the higher the blood pressure, the higher the risk of AD.[12] Low diastolic blood pressure (≤65 mm Hg) was also associated with increased risk of AD (relative risk [RR] 1.7) in a cohort of 1270 elderly patients during 6 years of follow up.[13] Antihypertensive treatment has been associated with preservation of cognitive function in elderly people with hypertension; risk of cognitive impairment was reduced by 38% (OR 0.62, CI 0.45 to 0.84) during 5 years of follow up in a longitudinal community survey.[40]

In a double-blind placebo-controlled trial of antihypertensive treatment for systolic hypertension, antihypertensive therapy reduced incidence of dementia by 50% after 2 years of follow up[30]; protection was even greater after the open-label continuation of the study (up to 3.9 years). The adjusted hazard rate (HR) associated with use of antihypertensives was 0.38 (CI 0.23 to 0.64). Based on these results, treating 1000 patients for 5 years could prevent 20 cases of dementia.[41,42]

Cholesterol and statins. High cholesterol levels have been implicated in pathogenesis of AD[43] and were identified as a risk factor for AD in epidemiologic studies. Cholesterol-reducing agents (statins) have been suggested to protect against development of AD.[44] Studies examining the association between plasma cholesterol levels and risk of AD and supporting use of cholesterol-lowering agents for preventing AD have been inconclusive so far.

In regard to treatment of patients with established AD, a randomized, double-blind trial of simvastatin in 44 normocholesterolemic patients showed reduction in beta-amyloid levels in cerebrospinal fluid and less cognitive decline measured by Mini-Mental State Examination (MMSE) scores in those receiving simvastatin.[45] We need more evidence from RCTs, however, to support use of lipid- and cholesterol-lowering agents exclusively for preventing AD.

Diet. Several prospective studies found associations between intake of dietary fats and risk of AD. High intake of saturated and transunsaturated (hydrogenated) fats was positively associated with increased risk of AD; intake of polyunsaturated and monounsaturated fats protected against cognitive decline in elderly people.[46-48] In a 4-year follow up of 980 elderly people, risk of AD was higher among those with high fat and calorie intake who had the APOE e4 allele.[49] The n-3 fatty acids contained in fish oils might reduce inflammation in the brain and might help regeneration of nerve cells.[50,51] They can potentially lower the risk of cardiovascular disease when combined with nonhydrogenated unsaturated fats, whole grains, fruit, and vegetables[52] and might consequently lower the risk of AD through vascular mechanisms. A recent Cochrane review[53] concluded, however, that it is unclear whether omega-3 fats affect cardiovascular events. More high-quality trials are needed.

Antioxidants, such as vitamins E and C and beta-carotene, might help protect against oxidative damage (part of the pathology of AD) by neutralizing free radicals. Lower levels of antioxidants were observed in people with AD in cross-sectional studies.[2] Prospective studies provide evidence of efficacy, but results are conflicting. In a prospective cohort study, high intake of vitamins C and E was associated with lower risk of AD in a cohort of 5395 participants older than 55 years at baseline.[54] In another study, high intake of vitamin E only from food, not from supplements, was associated with lower risk of AD.[55] A third prospective study showed that neither dietary nor supplemental

intake of carotenes, vitamin E, or vitamin C was associated with risk of AD.[56] Large clinical trials are under way to determine the value of antioxidants in prevention of AD.

Moderate wine or alcohol consumption has been identified in many prospective studies[57] as a protective factor, decreasing risk of dementia and AD. In a population-based study in Bordeaux, France, drinking three or four glasses of wine daily was associated with reduced incidence of dementia (OR 0.19) and AD (OR 0.28). We do not know, however, whether the wine per se is beneficial or whether it is a marker of people who are moderate in many things or who eat a healthier diet. Considering the high risk of addiction and negative consequences of alcohol consumption, perhaps we should avoid advising people who do not drink to start drinking.[57]

We should probably consider dietary intake as a whole, rather than focusing on individual foods. Although dietary recommendations still need to be further evaluated in controlled clinical trials specific to cognition or prevention of AD, they are likely to be in accordance with recommendations for lowering cardiovascular risk and might be extrapolated to prevention of cognitive impairment. Higher consumption of fish and healthy fats in vegetable oils and nuts and lower intake of saturated fat in meat and dairy products are likely desirable, as is consumption of fruit and vegetables that contain antioxidants. Avoiding obesity, and thus reducing risk of hypertension, will likely help as well.[58]

New learning

Frequent participation in stimulating activities (such as reading newspapers, watching television, playing cards, and doing crossword puzzles) was associated with reduced risk of AD in elderly people over 4.0 to 4.5 years of follow up in two studies.[59,60] People doing few cognitive activities (10th percentile) were twice as likely to develop AD as those frequently involved in such activities (90th percentile). Controlling for years of education and occupation did not strongly affect the magnitude of the association. Although reduced cognitive activity could be an early sign of AD, the association persisted after controlling for episodic memory impairment at baseline.

Physical activity

Physical exercise might protect the brain through various mechanisms, such as reducing cardiac disease, stroke, and diabetes mellitus, and increasing cerebral blood flow.[61] A recent meta-analysis showed that exercise improved cognitive function in elderly people with already established cognitive impairment or dementia.[62]

Evidence also suggests that physical activity protects against cognitive decline. Several longitudinal studies have found a positive relation between self-reported exercise and subsequent reduction in cognitive decline. In the Canadian Study of Health and Aging (a prospective cohort study), regular physical activity, compared with no exercise, was associated with lower risk of cognitive impairment, Alzheimer disease, and dementia of any type. High levels of physical activity reduced incidence of AD by half (OR 0.5, CI 0.28 to 0.98).[63] A prospective study of a rural community sample of 1146 elderly people showed that high exercise levels at baseline protected against decline in cognitive function as measured by MMSE scores at follow up.[61] Long-term regular activity, including walking, was associated with better cognitive function and less cognitive decline in 18 766 women aged 70 to 81 years in the Nurses' Health Study.[64] A 7-year prospective study in Japan also found that physical activity protected against AD.[65]

A study by Schuit et al[66] found that elderly people who did less than an hour of physical activity daily (compared with those who did more than an hour) had a twofold increase in risk of cognitive decline. Risk of cognitive decline increased 13.7 times (CI 4.2 to 45.5) in APOEe4 allele carriers who did less than an hour of physical activity daily.

Pharmacologic preventive approaches

Estrogen. Estrogen has a range of neuroprotective and neurotrophic effects in the parts of the brain involved in learning and memory. A recent meta-analysis that included 14 observational studies[67] showed that HRT protected against development of AD (OR 0.56, CI 0.46 to 0.68). A large, randomized, double-blind, placebo-controlled clinical trial of postmenopausal HRT, the Women's Health

Initiative (WHI), however, did not confirm these results. In the WHI Memory Study that enrolled participants from WHI, women taking estrogen (both combined estrogen-progestin and estrogen alone) were twice as likely to have dementia as those in the placebo group after 4 years of follow up (HR 2.19, CI 1.25 to 3.84).[68] Cardiovascular events, such as increased risk of stroke, associated with estrogen use might have contributed to the increased risk of dementia and might have overcome the potential protective effects of estrogen on cognition.

Zandi et al[69] recently reported results from an observational prospective study of 1889 elderly women and found that earlier use of HRT for at least 10 years was associated with reduced risk of AD (HR 0.41, CI 0.17 to 0.86), suggesting that HRT plays a role in reducing risk of AD if it is used during the menopausal transition, but not later. This would be consistent with trials that demonstrated that HRT is ineffective in delaying cognitive decline in women with established AD.[70] To date, there is insufficient evidence to support use of HRT for prevention of AD.

Nonsteroidal anti-inflammatory drugs (NSAIDs). A systematic review and meta-analysis of observational studies that included six cohort (total of 13 211 participants) and three case-control (total of 1443 participants) studies found a pooled RR of AD of 0.72 (CI 0.56 to 0.94) among users of NSAIDs. Long-term users' (>24 months) RR was 0.27 (CI 0.13 to 0.58). The pooled RR among users of acetylsalicylic acid in eight studies was 0.87 (CI 0.70 to 1.07).[71] Evidence suggests NSAIDs offer some protection against AD when taken long term, but there are as yet no results from RCTs establishing efficacy for prevention of AD, and the appropriate dose, duration of use, starting age, and appropriate population(s) for NSAID use remain unclear.[72]

Vitamin E. Based on its antioxidant property, vitamin E could have a role in preventing AD. Supportive evidence for this role came from the Alzheimer's Disease Cooperative Study, which evaluated the effects of 10 mg of selegiline or 2000 international units (IU) of vitamin E, or both together, as treatment for AD. Based on these results, many practitioners added vitamin E to treatment regimens for AD. The study reported delayed disability and delayed nursing home placement associated with vitamin E use, suggesting that vitamin E could slow progression of already established AD.[73]

Whether these results could be reproduced was questioned because the study was restricted to moderate AD, and the severity of AD was not homogeneous in the groups. A Cochrane review concluded, after adjusting for differences in groups of patients, that there was insufficient evidence to recommend vitamin E in treatment of AD.[74] A recent meta-analysis of randomized trials evaluating use of antioxidant supplements in prevention of gastrointestinal cancer found that use of beta-carotene, vitamin A, and vitamin E was associated with higher mortality.[75] There is currently insufficient evidence to support use of vitamin E for treatment or prevention of AD, and further studies are needed.[76,77]

Ginkgo biloba. A recent Cochrane review[78] found promising evidence of improvement in cognition associated with *Ginkgo biloba* in patients with dementia or cognitive impairment. The most recent studies, however, have inconsistent results, and a larger trial is needed to provide stronger evidence supporting use of *Ginkgo biloba* in treatment of dementia. Besides, serious side effects, such as coma, bleeding, and seizures, have been reported.[77] There is no evidence so far that *Ginkgo biloba* is useful in preventing AD.

Recommendations

As yet, no pharmacologic interventions have enough evidence to support their use in preventing AD. There are, however, some preventive approaches with various levels of evidence supporting them (**Table 2**). Medical workup can identify modifiable risk factors, such as hypertension, thyroid dysfunction, and hypercholesterolemia. Preventing new episodes of major depression (maintenance therapy with antidepressants) in those with recurrent mood disorders is desirable. Having a healthy lifestyle with regular physical activity, having ongoing learning experiences, and preventing traumatic brain injury seem to decrease risk of AD.

Table 2. Evidence supporting preventive approaches for Alzheimer disease and dementia

APPROACH	TYPE OF SUPPORTING EVIDENCE	LEVEL OF EVIDENCE
Physical activity	Prospective longitudinal studies	II
Ongoing learning	Prospective longitudinal studies	II
Preventing traumatic brain injury	Retrospective case-control study	II
Dietary recommendations	Prospective longitudinal studies	II
Cholesterol control	Cross-sectional studies	II
Blood pressure control	Randomized clinical trial	I
Treating thyroid disturbances	Cross-sectional studies	II
Prophylaxis of new episodes of depression for those with history of major depression	Prospective longitudinal studies	II

Conclusion

It is essential that health professionals educate patients about preventive strategies and potentially modifiable risk factors for AD, especially patients at higher risk of AD. While medical care and having a healthy lifestyle can decrease risk of AD, more research is needed to further investigate the effectiveness of specific preventive strategies.

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Contributors

Drs Scalco *and* **van Reekum** *contributed to concept and design of the study, analysis and interpretation of data, and preparing the paper for publication.*

Competing interests

None declared

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EDITOR'S KEY POINTS

- Given the growing population of elderly people and the concomitant increase in prevalence of Alzheimer disease (AD), family physicians should be aware of strategies that could delay or prevent onset of AD.
- There is no evidence that screening for AD in the general population is effective, but among patients at higher risk, such as those with a family history of AD who are concerned about AD and those complaining of memory problems, cognitive testing should be considered.
- Patients presenting with memory difficulties who test positive for mild cognitive impairment are at increased risk of developing AD at a rate of about 10% annually. Neuroimaging has shown some structural markers, but they are not specific enough to be useful. Certain genetic defects have a higher predictive value for AD, but the value is still too low for screening the general population.
- There is good evidence that blood pressure control could prevent development of AD and that estrogens do not reduce the incidence of AD. Observational studies suggest that a healthy diet, exercise, new learning experiences, and cholesterol control help prevent AD.

POINTS DE REPÈRE DU RÉDACTEUR

- Le vieillissement de la population et l'augmentation concomitante de la prévalence de la maladie d'Alzheimer (MA) devraient inciter le médecin de famille à se renseigner sur les stratégies susceptibles de retarder ou de prévenir l'apparition de cette maladie.
- L'efficacité d'un dépistage systématique de la MA n'a pas été démontrée; toutefois, chez les patients à risque élevé, comme ceux qui s'inquiètent à cause d'une histoire familiale de MA et ceux qui se plaignent de troubles de mémoire, certains tests cognitifs devraient être envisagés.
- Le patients qui ont des troubles de mémoire et dont les tests révèlent des pertes cognitives mineures risquent davantage de développer la MA à un taux d'environ 10 % par année. Même si la neuro-imagerie a révélé certains marqueurs structuraux, cette technique n'est pas suffisamment spécifique pour être utile. Certains défauts génétiques sont de meilleurs facteurs prédictifs de la MA, mais leur valeur est encore insuffisante pour justifier un dépistage systématique.
- Certaines données valables indiquent que le contrôle de la tension artérielle pourrait prévenir le développement de la MA, alors que les oestrogènes n'en réduisent pas l'incidence. D'après les études observationnelles, une alimentation saine, de l'exercice, de nouvelles expériences d'apprentissage et un contrôle du cholestérol aident à prévenir la MA.

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